Association of molecular subtypes with MR perfusion parameters in patients with brain meningioma

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Abstract:

Background and Objective: Meningiomas are the most common primary brain tumors, accounting for 15 to 20% of all primary brain tumors. Differentiating between malignant and benign meningiomas before surgery is essential for treatment planning and prognostic assessment. One proposed method for differentiating malignant from benign meningiomas is magnetic resonance perfusion (MR perfusion); however limited studies have been conducted in this area. Therefore, this study aimed to investigate the relationship between molecular subtypes and MR perfusion in patients with meningiomas.

Materials & Methods: In this cross-sectional study, all patients with brain meningiomas referred to Sina Hospital in Tehran between 2021 and 2024 were prospectively evaluated. MR perfusion imaging was performed for all patients. Following brain surgery, pathological samples were obtained, and in addition to determining the conventional tumor grade, molecular analyses- including Ki-67, EGFR amplification, and S100 were conducted by the pathologist, with the results were recorded. The relationship between MR perfusion parameters (relative cerebral blood volume (rCBV), relative cerebral blood flow (rCBF), and mean transit time) and tumor-related data was assessed. A significance level of $p < 0.05$ was considered statistically significant.

Results: Twenty-five patients were studied. The mean age was 55.08 ± 12.07 years, and 17 patients (68%) were female. The most common presenting symptom was headache (76%). The findings showed that rCBV and rCBF differed significantly between low-grade and high-grade tumors ($P < 0.05$). Although the calculated cut-off values for rCBV and rCBF (7.55 and 6.94, respectively) were useful for differentiating tumor grades, neither reached statistical significant ($P= 0.05$ and $P= 0.1$, respectively). Additionally, patients with higher Ki-67 levels exhibited higher rCBV and rCBF values ($P < 0.05$ for both).

Conclusion: MR perfusion values (rCBV and rCBF) show statistically significant differences among different grades of meningioma.

Keywords: perfusion Magnetic resonance imaging; Meningioma; brain neoplasms; biomarkers, tumor

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Background and Objective

Meningiomas are the most common type of intracranial tumor, accounting for 30% of all primary brain neoplasms. These tumors primarily affect middle-aged individuals and are thought to originate from arachnoid cap cells[1,2].

While the majority of meningiomas are classified as benign, it is important to note that up to 20% of these tumors are atypical or malignant. These variants tend to be more aggressive and have a higher likelihood of recurrence. The extent of initial tumor resection, combined with the histological grade, serves as a significant predictor of tumor recurrence. Therefore, understanding the histological grade prior to surgery is essential for effectively planning surgical interventions and radiotherapy [3,4].

The risk of meningioma recurrence has traditionally been associated with the World Health Organization (WHO) histopathological grade and the extent of surgical resection. However, recent studies have highlighted the significance of molecular characteristics in assessing meningioma aggressiveness and recurrence risk. Investigating the relationship between these molecular subtypes and preoperative imaging findings can improve patient management. The standard diagnostic approach for meningioma involves brain magnetic resonance imaging (MRI), with or without intravenous contrast. While this method is generally effective in detecting meningiomas, conventional MRI sequences often do not differentiate between various typical meningioma subtypes, or between typical, atypical, and malignant meningiomas[5-7]. Magnetic resonance perfusion (MR perfusion) has the potential to help distinguish primary neoplastic processes from other masses. Nevertheless, there is limited research exploring the correlation between the molecular subtypes of brain meningiomas and MR perfusion findings. Therefore, the objective of this study was to investigate the relationship between meningioma molecular subtypes and MR perfusion parameters[5,8-10].

Materials and Methods

This cross-sectional prospective study that was conducted on all patients with brain meningiomas referred to Sina Hospital in Tehran between 2021 and 2024. All patients presenting with newly diagnosed brain meningioma who were candidate for surgical intervention and referred to Sina Hospital were included. The exclusion criteria were :age under 18 years or over 75 years; lack of prior care at this center; incomplete medical records; refusal to consent to participate; psychological disorders; concurrent malignant diseases; pregnancy; concurrent brain lesions other than meningioma; history of stroke; previous brain surgery; recurrent meningioma; multiple meningiomas; history of neurofibromatosis; meningiomas secondary to radiotherapy; prior adjuvant therapy for meningioma before surgery; requirement for emergency surgery for meningioma; Karnofsky Performance Status (KPS) less than 70; and modified Rankin Scale (mRS) greater than 2.

Following evaluation against the predefined criteria, eligible patients who met the inclusion criteria underwent brain MR perfusion imaging after hospitalization. The imaging data were processed and analyzed at the Imaging Center of Imam Khomeini Hospital, Tehran University of Medical Sciences.

Brain MR perfusion was conducted at the hospital utilizing a General Electric Discovery 750 GEM 3-Tesla device. To facilitate coordination and analysis, a member of the Radiology Department collaborated as a collaborative partner on the project.

The patients were examined by a neurosurgeon, during which demographic information was systematically recorded using a checklist. Subsequently, surgical procedures were performed on the patients. Following surgery, conventional tumor grading was conducted alongside molecular assessments, including ki-67, epidermal growth factor receptor (EGFR) amplification, and S100. These analyses were carried out by a hospital pathologist, and the findings were thoroughly documented.

All tumor-related pathological data were independently reviewed and recorded by two pathologists. All MR perfusion (MRP) procedures were performed in collaboration with the Imaging Department of Imam Khomeini Hospital. The imaging findings for each patient were subsequently received, analyzed, and archived. Upon completion of the study, all patient data were thoroughly reviewed, and the final analysis was conducted.

Using the repeated-measures formula and related statistical calculations, with a Type I error rate of 5% and a study power of 80%, and based on findings from previous studies, the minimum required sample size for this study was initially estimated to be 45 participants. After accounting for an anticipated dropout rate of at least 10%, the adjusted required sample size was approximately 50 participants. However, due to the limited number of referrals to Sina Hospital, the small pool of eligible patients, the high cost of laboratory tests, and financial constraints, the final sample size was set at 25 patients, with the approval of the department's Vice Chancellor for Research.

Statistical Methods

The collected data were analyzed using SPSS version 26 software. Descriptive statistics, including the mean and standard deviation for continuous variables and frequency (number and percentage) for categorical variables, were used to summarize the data. One-way ANOVA with pairwise Bonferroni post hoc test was used to examine the differences between groups for continuous variables. A p-value of less than 0.05 was considered statistically significant.

Ethical considerations

This study was approved by the Ethics committee of Tehran University of Medical Sciences (IR.TUMS.SINAHOSPITAL.REC.1401.054).

Findings

Twenty-five patients were evaluated. The mean age of the participants was 55.08 ± 12.07 years; 32% were male (n = 8), and 68% were female (n = 17). Data on presentation, tumor location, and tumor type are presented in Table 1.

Clinically, headache was the most prevalent symptom, observed in 19 patients (76%). Additional symptoms included visual loss in 4 patients (16%), seizures in 1 patient (4%), and limb weakness in 1 patient (4%). Regarding tumor type, meningothelial and atypical meningiomas were most common, each accounting for 8 cases (32%). Transitional meningioma was identified in 6 cases (24%), and anaplastic meningioma in 3 cases (12%). According to the Traditional Grading System, 12 patients (48%) were classified as grade 1, 10 patients (40%) as grade 2, and 3 patients (12%) as grade 3. Tumor location data are presented in Figure 2.

Ki-67 was greater than 10% in 4 patients (16%), between 5% and 10% in 1 patient (4%), and less than 5% in 20 patients (80%). Among patients with Grades 1, 2, and 3, 9 patients (75%) had Ki-67 levels below 5%, three patients had Ki-67 levels greater than 10%, and one patient had Ki-67 greater than 10%, respectively. EGFR was negative in all patients, while S100 was strongly positive in only one patient with Grade 2 disease (4%).

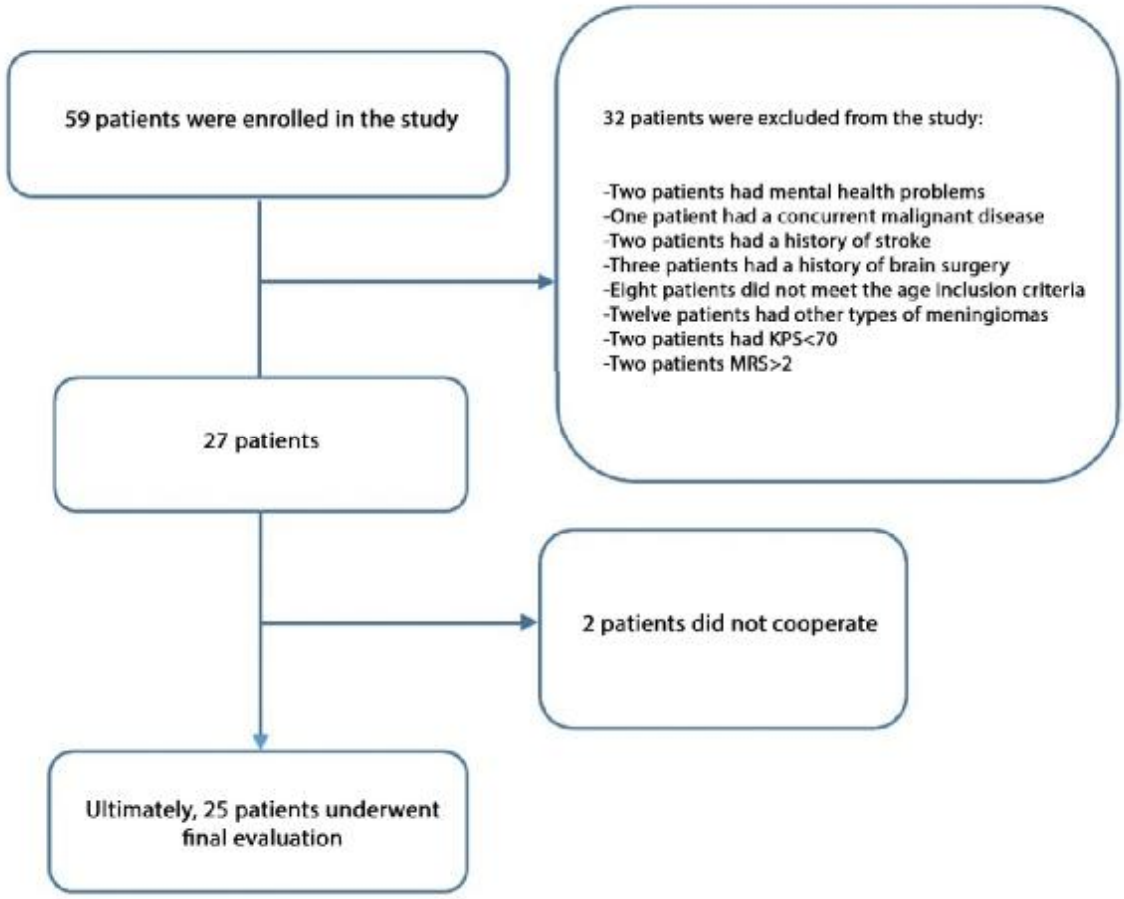

Diagram 1 - CONSORT chart

Table 1- Comparison of MRI perfusion parameters between different tumor grades

	Grade						
	1		2		3		
Variable	Mean	Standard Deviation	Mean	Standard Deviation	Mean	Standard Deviation	Probability Value
rCBV	6.96	2.36	7.33	2.72	29.00	2.00	<0.001
rCBF	4.52	1.73	16.39	23.95	44.67	6.03	0.001
MTT (Sec)	17.63	9.26	17.06	11.01	23.67	4.04	0.573

P-value based on ANOVA (Pairwise comparison by Bonferroni Test)

The mean values of MR perfusion parameters, including rCBV, rCBF, and MTT, for all patients were 9.74 ± 7.64, 19.08 ± 13.61, and 18.15 ± 9.44, respectively.

Table 1 presents the association between Magnetic Resonance (MR) perfusion parameters and meningioma tumor grade. Both relative cerebral blood volume (rCBV) and relative cerebral blood flow (rCBF) demonstrated statistically significant correlations with tumor grade. In contrast, mean transit time (MTT) did not show a significant association with tumor grade.

The relationship between meningioma histological subtypes and MR perfusion parameters is summarized in Table 2. A statistically significant difference in rCBV was observed across the histological groups. Post hoc pairwise comparisons revealed that rCBV values were significantly higher in anaplastic tumors compared to all other subtypes ($P < 0.001$). Similarly, rCBF also differed significantly among the histological groups ($P = 0.005$). However, no statistically significant differences in MTT were detected among the histological subtypes (all $P > 0.05$).

To establish diagnostic cut-off values for meningioma grading, Receiver Operating Characteristic (ROC) analysis was performed. ROC curves were generated based on the parameters that showed significant differences between tumor grades, as detailed in Table 3. Due to the limited sample size of Grade 3 meningiomas (n=3), patients with Grade 2 and Grade 3 tumors were combined into a single “Grade 2/3” group for statistical analysis. Subsequent interpretations are based on the results derived from this combined cohort.

Interpretation of Relative Cerebral Blood Volume (rCBV) Cut-off Analysis Results

The area under the curve (AUC) for rCBV was 0.731, indicating a moderate to good level of diagnostic accuracy for grading differentiation based on rCBV measurements. The standard error associated with this AUC value was 0.106. The p-value was 0.050, which is at the threshold of statistical significance ($p \leq 0.05$). This result may be attributed to the limited sample size used in the analysis.

The optimal cut-off value of rCBV for detecting various grades of meningioma was 7.55.

In this Cut off:

Sensitivity: 83.3%, indicating that 83.3% of Grade 2/3 tumors were correctly identified.

Specificity: 30.8%, indicating that 30.8% of Grade 1 tumors were correctly identified.

A cut-off value of 7.55 for relative cerebral blood volume (rCBV) was assessed for its diagnostic performance in distinguishing Grade 1 from Grade 2/3 meningiomas. This proposed threshold of 7.55 for rCBV demonstrate high sensitivity (83.3%), indicating a strong ability to identify high-grade (Grade 2/3) meningiomas. However, its relatively low specificity (30.8%) suggests a substantial rate of false positives, meaning that a significant proportion of Grade 1 tumors may be incorrectly classified as Grade 2/3.

Interpretation of Relative Cerebral Blood Flow (rCBF) Cut-off Analysis

Receiver Operating Characteristic (ROC) analysis of relative cerebral blood flow (rCBF), conducted to differentiate Grade 2/3 meningiomas from Grade 1 tumors, yielded an area under the curve (AUC) of 0.692. This value indicates a moderate and clinically acceptable diagnostic performance of rCBF in this context. Although the associated p-value of 0.103 did not reach the conventional threshold for statistical significance, the AUC value exceeding 0.65, along with its 95% confidence interval (0.475–0.910), suggests that the diagnostic performance of rCBF may be considered promising. Using the Youden Index, which identifies the optimal balance between sensitivity and specificity, the most appropriate cut-off value for distinguishing Grade 1 from Grade 2/3 tumors was determined to be 6.94 ml/100 g/min.

Table 2- Comparison of cerebral perfusion parameters in different histopathological types of meningiomas

	Type								
	Anaplastic		Atypical		meningothelioma		transitional		
Variable	Mean	Standard Deviation	Mean	Standard Deviation	Mean	Standard Deviation	Mean	Standard Deviation	Probability Value
rCBV	29.00	2.00	8.01	0.83	6.92	2.25	5.16	3.21	<0.001
rCBF	44.67	6.03	20.00	26.32	5.05	1.26	3.86	2.37	0.005
MTT (Sec)	23.67	4.04	14.90	5.92	13.63	7.83	26.53	12.74	0.091

Table 3- Determining the cut-off of rCBV for tumor grade detection

Index	Value
area under the curve (AUC)	0.731
P-value for AUC	0.05
Cut-off based on Youden index	7.5500
Sensivity at thecut-off point	0.833
specifityat the cut-off point	0.308

Table 4- Results of determining the rCBF cut-off for tumor grade differentiation

Index	Value
Cut-off based on Youden index	6.49 ml/100g/min
Sensitivity	50%
Specificity	100 %100
AUC	0.692
P-value for AUC	0.103

At this threshold, specificity reached 100%, indicating that all Grade 1 tumors were correctly classified. However, sensitivity was 50%, meaning that only half of the Grade 2/3 tumors were identified accurately. Therefore, this cut-off may be particularly useful in settings where minimizing false-positive results is critical, such as preliminary screening or ruling out the presence of Grade 2/3 disease.

Overall, these findings suggest that rCBF may serve as a valuable adjunctive marker for differentiating meningioma grades, especially when interpreted in conjunction with other diagnostic parameters. Detailed results are presented in Table 4. The Receiver Operating Characteristic (ROC) curves for rCBV and rCBF are shown in Figures 3 and 4, respectively.

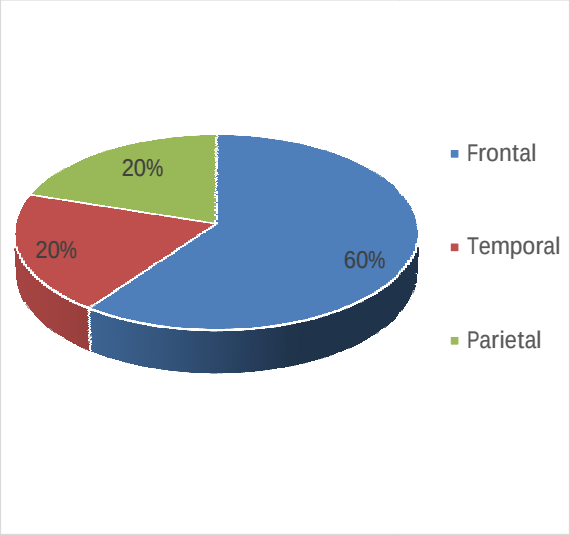

Diagram 2- Tumor location in the studied patients

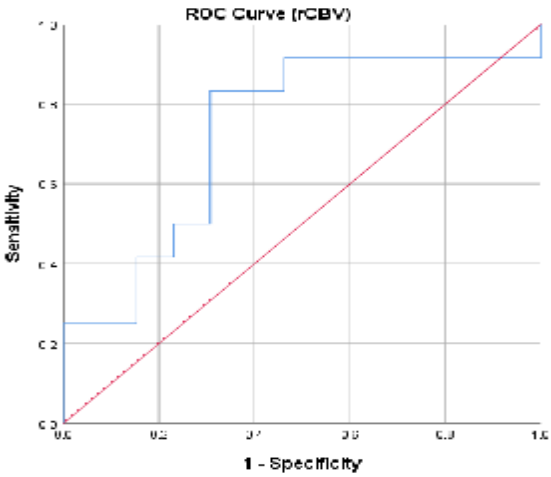

Diagram 3- ROC diagram for rCBV

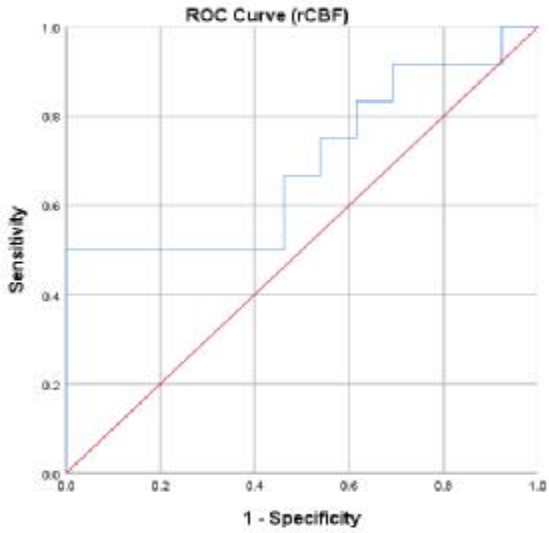

Diagram 4- ROC diagram for rCBF

Discussion

This study evaluated 25 patients with a mean age of 55.08 ± 12.07 years, of whom 17 patients (68%) were female. The mean Ki-67 was 0.06 ± 0.04, and headaches were the most common symptom, reported by 76% of participants. Grade 1 tumors were the most frequently operated on, accounting for 52% of the cases. rCBV and rCBF significantly increased with higher tumor grades, with anaplastic meningiomas exhibiting the highest values.

The study identified cut-off values for differentiating grade 1 from grade 2/3 meningiomas, with rCBV at 7.55 (sensitivity= 83.3%, specificity= 30.8%, P= 0.05) and rCBF at 6.94 (sensitivity= 50%, specificity= 100%, P= 0.1). However, neither cut-off reached statistical significance, likely due to the small sample size. A significant association was found between rCBV and rCBF with Ki-67 levels, indicating that higher Ki-67 levels were associated with higher rCBV and rCBF.

MRI is an crucial imaging modality for evaluating pathophysiological processes. In particular, the characterization of brain tumors has greatly benefited from advancements in techniques such as diffusion-weighted imaging (DWI) and perfusion imaging. However, despite the numerous computational methods that have been proposed, a comprehensive analysis of meningiomas remains lacking. Furthermore, MR perfusion parameters have been suggested as promising biomarkers for tumor staging[11,12].

In a study examining the role of MR perfusion using arterial spin labeling (ASL) and dynamic susceptibility contrast (DSC) in the grading of skull base meningiomas, Eissa et al. concluded that MR perfusion is effectively distinguishes between low-grade and high-grade meningiomas[13]. The findings of the present study support the utility of MR perfusion in diagnosing meningiomas. Our investigation revealed a significant association between meningioma grade and MR perfusion parameters, with rCBV and rCBF showing higher values in higher-grade tumors compared to lower- grade ones. Furthermore, the current study demonstrated that different meningiomas grades could be differentiated based on established cutoff values. However, it is important to note that the cutoff values for rCBV and rCBF did not reach statistical significance, which may be attributed to the limited sample size. This limitation underscores the need for further studies with larger cohorts to validate the proposed cutoff values.

Qiao et al. investigated the effectiveness of MR perfusion using ASL in differentiating benign from malignant meningiomas. They identified three perfusion patterns: Pattern 1 showed homogeneous hyperperfusion, associated with grade I meningiomas; Pattern 2 exhibited heterogeneous hyperperfusion; and Pattern 3 revealed no significant hyperperfusion, correlating with grade II and III meningiomas. The study concluded that qualitative assessment of cerebral blood flow (CBF) maps could assist in distinguishing benign from higher-grade tumors, potentially influencing treatment strategies.[14]

The current study found that rCBVand rCBFwere positively and significantly associated with increasing tumor grade. Although the mean transit time (MTT) was different between the groups, it was not statistically significant, possibly due to the small sample size.

The study conducted by Rohilla et al. assessed the grading of meningiomas by analyzing rCBV. The findings indicated that the maximum rCBV within the tumor did not significantly aid in distinguishing benign meningiomas from malignant ones. Notably, an rCBV threshold of 2.5 mL/100 g in peritumoral edema demonstrated a sensitivity of 75%, specificity of 84.6%, and an accuracy of 83.3% for differentiating between benign and malignant meningiomas. Consequently, the study concluded that benign and malignant meningiomas can be effectively differentiated based on the maximum rCBV in peritumoral edema. Nevertheless, intratumoral rCBV values may provide valuable insights into the subtyping of meningiomas, particularly in assessing transitional and meningothelial types[15].

In the current study, rCBV values were demonstrated a statistically significant association with menangioma grading, with higher rCBV values correlating with increased tumor grades. Both studies support the notion that rCBV may serve as a potential biomarker for meningioma grading, despite employing different methodologies. Although these methodological differences exist, existing research substantiates the diagnostic utility of MR perfusion imaging in assessing meningioma status. In our study, the diagnostic cutoff established for differentiating meningioma grades based on rCBV was established at 7.55, yielding a sensitivity of 83.3% and a specificity of 30.8%. The discrepancies between our findings and those reported by Rohilla et al. may be attributed to differences in the target sites for rCBV measurement; our study focused on the tumor itself, whereas Rohilla et al. examined the peritumoral edema.

Previous research has indicated that the evaluation site, imaging device type, and the software used can significantly influence MR perfusion parameter values, which may explain the variability observed across studies[16,17].

Pond et al. investigated preoperative magnetic resonance imaging (MRI) features of intracranial chordoid meningiomas (WHO Grade II) to identify distinctive characteristics that could differentiate this subtype from other meningioma variants. Their findings demonstrated that chordoid meningiomas exhibited significantly elevated apparent diffusion coefficient (ADC) and normalized ADC values compared with other meningioma grades (I, II, and III), enabling reliable preoperative prediction of this atypical histopathological diagnosis[18]. A key distinction between the present study and that of Pond et al. is that ADC measurements were not included in our analysis. Nevertheless, our study included all meningioma subtypes, providing a broader analytical scope. Despite these methodological differences, our findings align with prior evidence supporting the diagnostic value of MRI in meningioma evaluation. Perfusion MRI and ADC are complementary techniques that assess distinct tissue characteristics. Perfusion MRI evaluates blood flow and microvascularity, whereas ADC reflects the diffusion of water molecules, providing information about tissue microstructure and cellularity[19-21]. Future studies should aim to compare the relative diagnostic accuracy and grading performance of these modalities in meningioma assessment.

Lum et al.'s study aimed to evaluate the efficacy of Intra-Arterial (IA) MR perfusion in characterizing the vascular supply of meningiomas. The findings indicated that Full Width at Half Maximum (FWHM), rCBV, and rCBF showed statistically significant differences between Regions of Interest (ROIs) for IA MR perfusion. Moreover, rCBV and MTT were significantly lower for IA perfusion in the Dural External Carotid Artery (ECA) compared to intravenous (IV) perfusion, while rCBF was notably higher in the Internal Carotid Artery (ICA) region for IA MR[22].

The current study demonstrates that MR perfusion can effectively differentiate between different grades of meningioma, highlighting its diagnostic utility for preoperative assessment. Although MTT did not show significant differences among grades, the parameters of rCBV and rCBF proved valuable due to their sensitivity and specificity. This comparison suggests that MR perfusion is a promising imaging technique for grading meningiomas; however, further studies are necessary to confirm its diagnostic value. while other studies have investigated the utility of MR perfusion parameters, they did not evaluate the specific parameters examined in our study. In this respect, our findings align with previous research regarding the importance of MR perfusion in relation to the pathological features of meningiomas.

In our study, Ki-67expression was observed to increase with escalating tumor grades from 1 to 2 and 3, particularly noted in grades 2 and 3, where a higher proportion of patients exhibited elevated Ki-67 levels. However, it is important to note that the small sample size precluded establishing statistical significance. Numerous studies have indicated that Ki-67 serves as an independent prognostic indicator for meningioma[23-25]. Nevertheless, the prognostic implications of Ki-67 in meningioma remain inconclusive. Some research has identified a negative correlation between Ki-67 expression levels and meningioma prognosis, while other investigations have reported non-significant findings. These discrepancies may be attributed to the substantial differences in the cut-off values used for Ki-67 analysis, the definitions of these cut-off values, and the tumor grades considered across studies[26-28]. Our findings indicate a statistically significant association between rCBF and Ki-67. This observation aligns with the study conducted by Ginat et al., which reported a positive and statistically significant relationship between maximum rCBV and Ki-67. Notably, our investigation reveals that no previous studies

have assessed the association between Ki-67 and rCBF, underscoring the need for further research in this area and highlighting the novelty of this evaluation in the present study.

Implementation Constraints and Mitigation Strategies

One significant limitation of this study was the small sample size, which resulted from the low prevalence of meningioma. Additionally, our center is a referral facility, and most referred patients present with complicated cases. The majority of tumors were falx and parasagittal meningioma, which may explain the high proportion of grades 1 and 2 tumors observed. While other molecular and genetic tests could potentially correlate with MR perfusion parameters, we were unable to investigate these factors due to their inaccessibilty and high cost.

Conclusion

The values of MR perfusion parameters, including rCBV and rCBF, demonstrate statistically significant differences between different grades of meningioma. These parameters may serve as potential preoperative diagnostic tools to improve the management of patients presenting with these tumors. According to our findings, the established differential cutoffs for rCBV and rCBF were 7.55 and 6.94, respectively. While these cutoffs demonstrated commendable sensitivity and specificity for diagnosing meningioma grades, they were not statistically significant, possibly due to the small sample size used in this study.

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